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Combatting COVID19: The Critical Role of Nonhuman Primate Research

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COMBATTING COVID19: THE CRITICAL ROLE OF NONHUMAN PRIMATE RESEARCH

December 10, 2020

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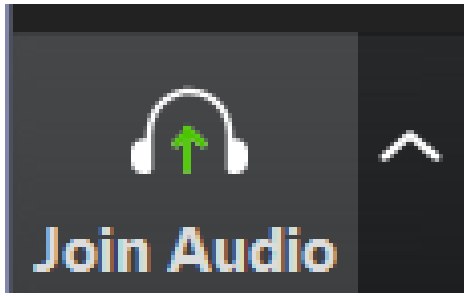

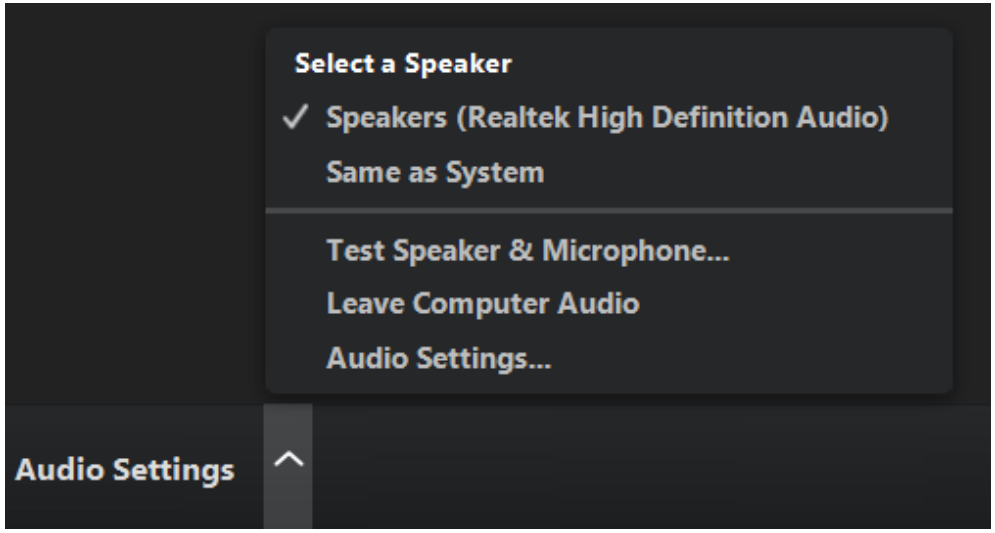

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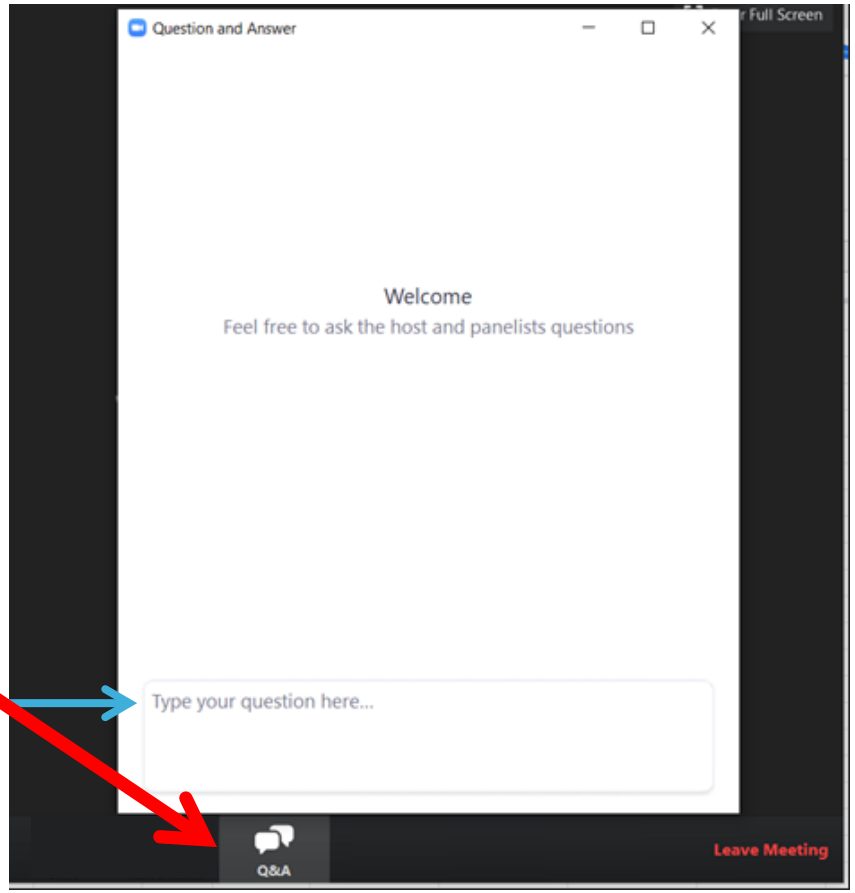
Type your question in the box



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Speakers

Jay Rappaport, PhD

Director and Chief Academic Officer
Tulane National Primate Research Center.
Tulane School of Medicine

Nancy Haigwood, PhD

Professor and Director
Oregon National Primate Research Center,
Oregon Health & Science University

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FASEB DISCUSSION: SARS-COV-2 RESEARCH

December 10th, 2020

Jay Rappaport, Ph.D., Director and Chief Academic Officer,

Tulane National Primate Research Center
Covington, LA

CoVID19 Research Update

- **One Nonhuman Primate Study: Three Papers**

  Robert Blair: Pathology

  Monica Vaccari: Monocytes/Macrophages and Cytokines

  Tracy Fischer: CNS Pathology

- **Passive Antibody Studies**

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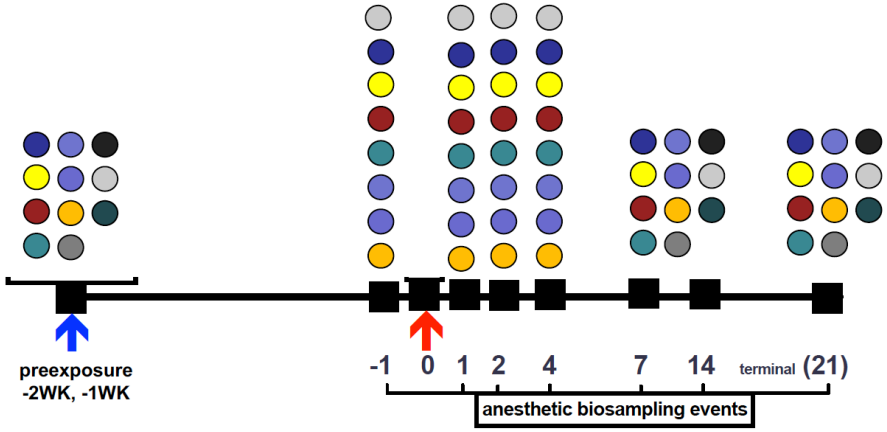
SARS-CoV-2 NHP model development



***M. mulatta* (Indian origin)** **C. aethiops**

experimental infection

initial ➡ **(IT, oral, IN, ocular)**

2^{o} ➡ **aerosol**

- **blood collection**
- **urine**
- **stool (Loop)**
- **PE & Temp**

- **BAL (80mL)**
- **bronchial brush**
- **mucosal fluid/swabs**
- **CSF**

- **PET/CT**
- **plethsymography / respiratory**
- **chest X-ray**

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American Journal of Pathology: In Press

"Acute Respiratory Distress and Cytokine Storm in Aged, SARS-CoV-2 Infected African Green Monkeys, but not in Rhesus Macaques"

Robert V. Blair, Monica Vaccari, Lara A. Doyle-Meyers, Chad J Roy, Kasi Russell-Lodrigue, Marissa Fahlberg, Chris J. Monjure, Brandon Beddingfield, Kenneth S. Plante, Jessica A. Plante, Scott C. Weaver, Xuebin Qin, Cecily C. Midkiff, Gabrielle Lehmicke, Nadia Golden, Breanna Threeton, Toni Penney, Carolina Allers, Mary B Barnes, Melissa Pattison, Prasun K Datta, Nicholas J Maness, Angela Birnbaum, Tracy Fischer, Rudolf P. Bohm, Jay Rappaport

doi: https://doi.org/10.1101/2020.06.18.157933

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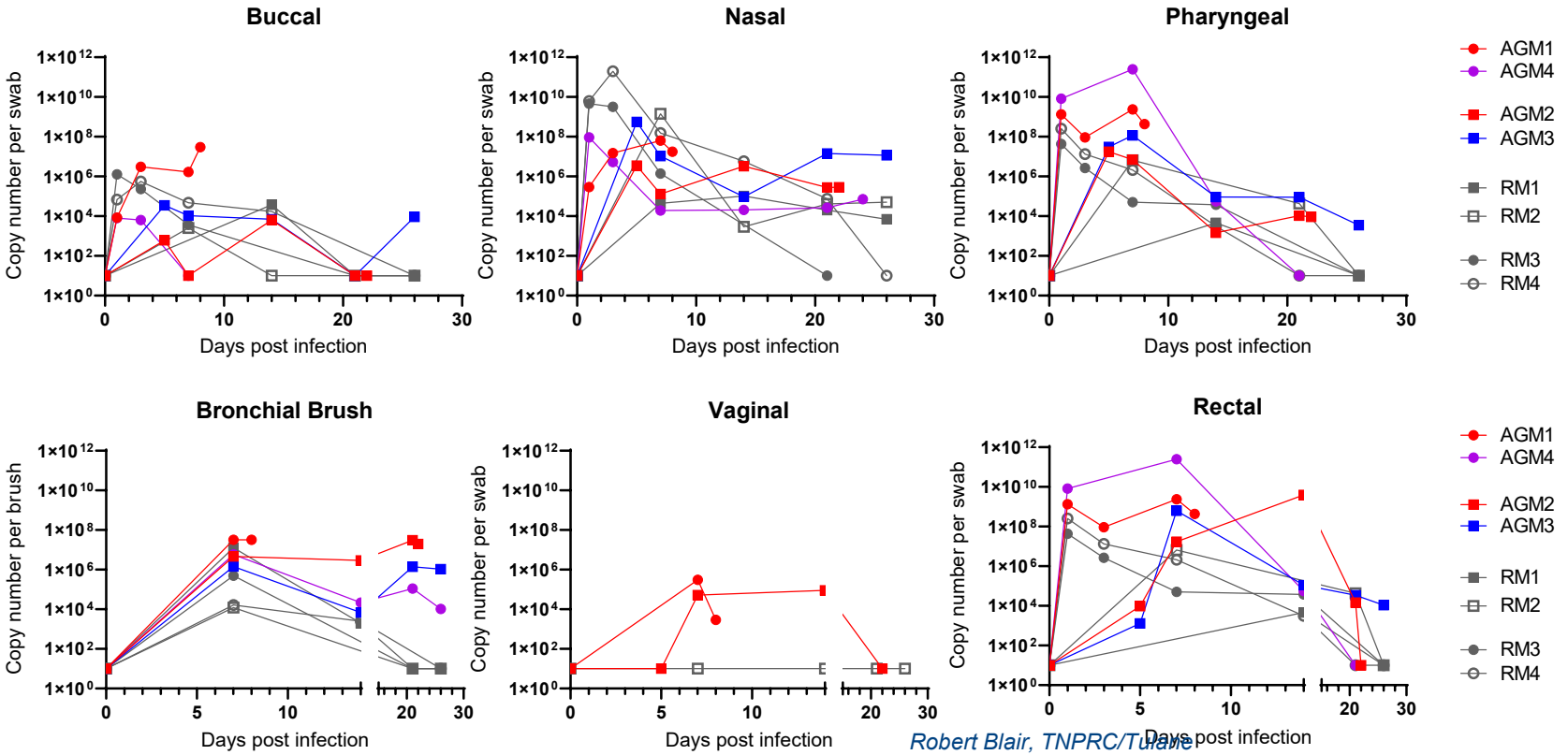
Quantification of viral loads from mucosal swabs



Robert Blair, TNPRC/Tulane

All animals (4 African green monkeys and 4 rhesus macaques) had detectable virus at mucosal sites. No significant differences were noted in viral load between species and route of exposure (Mann-Whitney U test). Animals with ARDS trended to high viral loads in bronchial brush samples.

Circles: aerosol exposure; Squares: multi-route exposure; **Gray**: Rhesus macaques; Color: AGM by outcome. **Red**: developed ARDS; **Purple**: increased cytokines without ARDS; **Blue**: no cytokine increase or ARDS.

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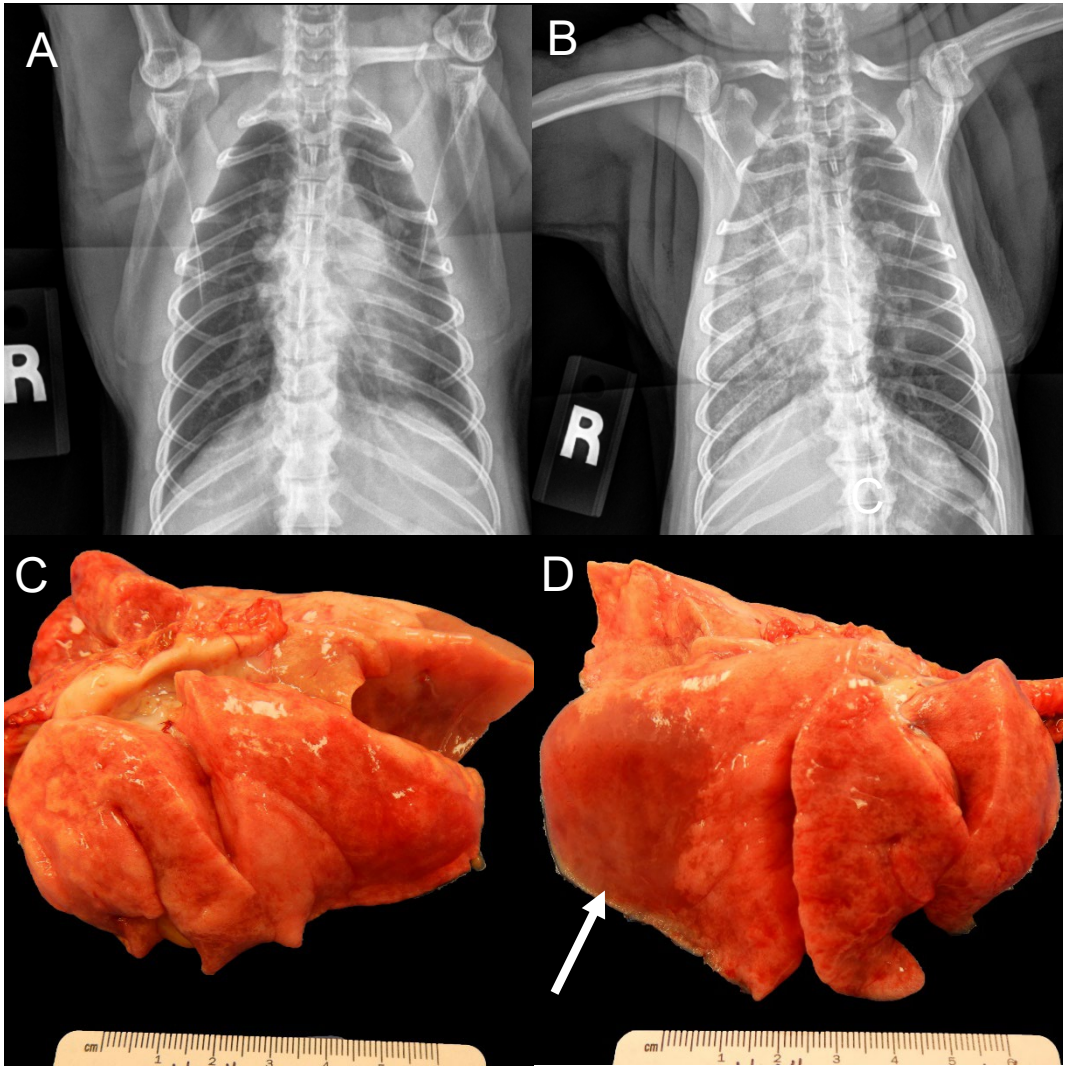
Pathologic changes in CoV-2 exposed African Green Monkeys



Radiographs 22 hours before **(A)** and at the time of necropsy **(B)** showing the rapid development of alveolar lung opacities throughout the right lung lobes.

C) The left lung lobes fail to collapse.

D) There is extensive consolidation of the right lower lung lobe with pulmonary edema (arrow). The right middle and anterior lobes are less affected. On cut surface all lobes ooze copious fluid.

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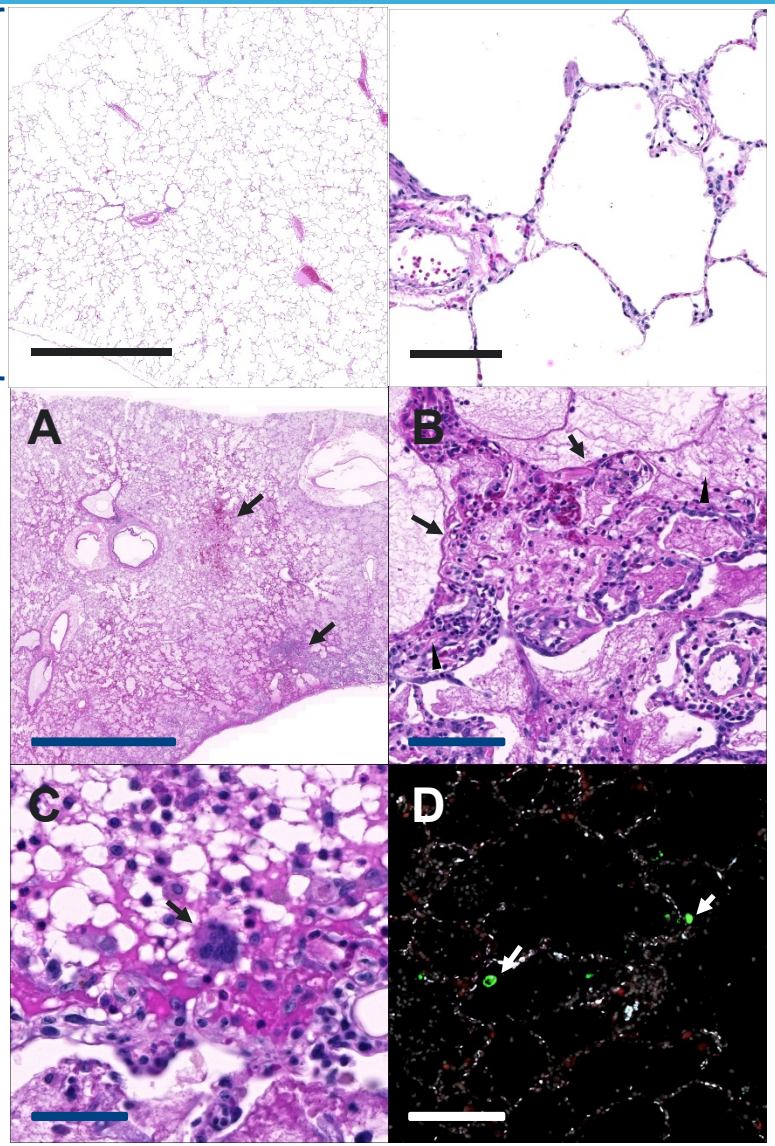
Histopathology and fluorescent IHC in AGM1

Normal

AGM1



A) The right lower lung lobe is filled with fibrin and edema with areas of hemorrhage and necrosis (arrows)

B) Alveoli are variably lined by hyaline membranes (arrows) and type II pneumocytes (arrowheads)

C) Rare multinucleated syncytia (arrow) are scattered throughout the affected lungs

D) Fluorescent immunohistochemistry for COV-2 nucleoprotein (green, arrows) and ACE2 (red) identified low numbers of CoV-2 positive cells within the affected lung lobes; White: DAPI/nuclei; Green: CoV-2; Red: ACE2 Blue: Empty.

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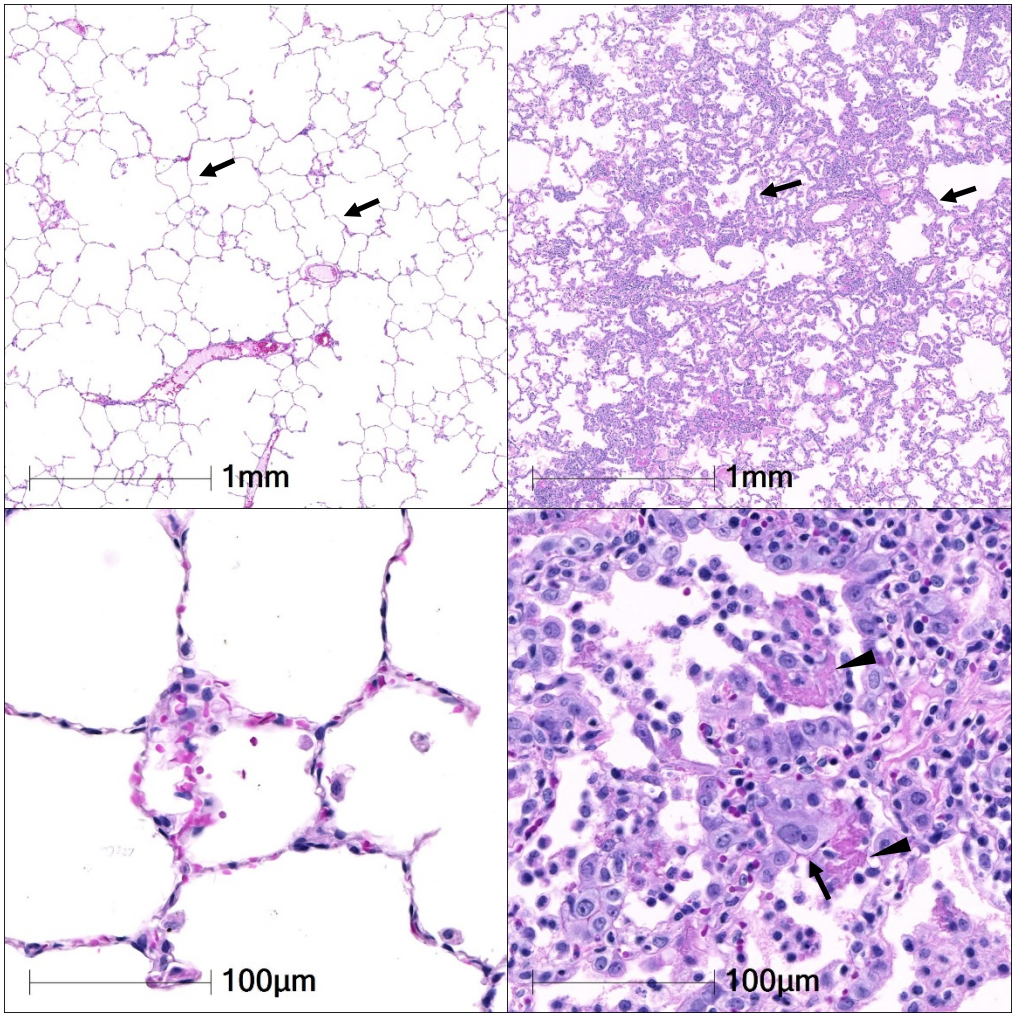
Acute Lung Injury in Rhesus Macaque: 7 days post-infection

Top: Compared to normal lung (left), the alveolar septae (arrows) of infected macaques (right) are markedly thickened with infiltration by a mixed inflammatory cell population. (2x objective).

Bottom: Alveoli of SARS-CoV-2 infected macaques (right) are lined by type pneumocytes that occasionally atypia (arrow) and contain inflammatory cells and fibrin (arrowheads)(20x objective).



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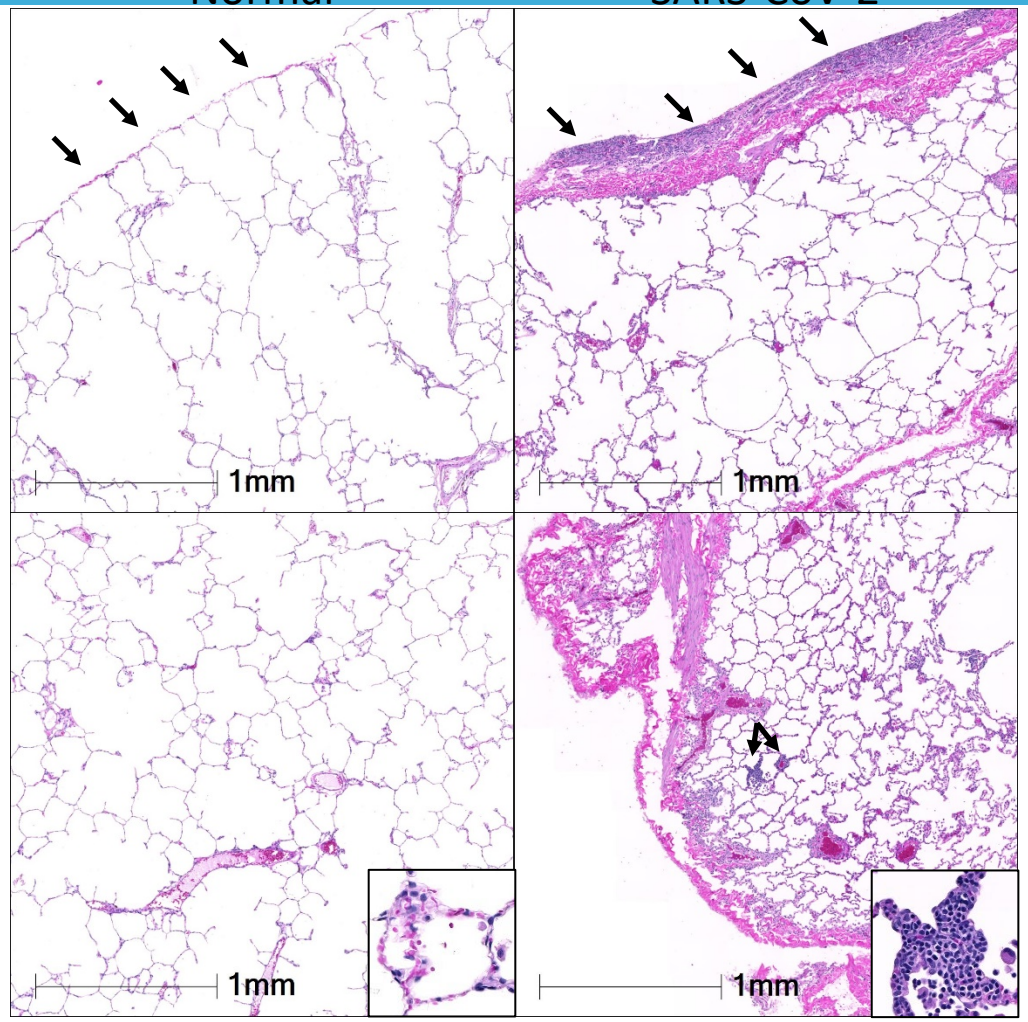
Acute Lung Injury in Rhesus Macaque: 30 days post-infection

Top: Infected animals (right) develop multifocal pleuritis and pleural adhesions, with marked thickening of the affected pleura (arrows). 2x objective.

Bottom: There are scattered foci of residual pulmonary interstitial inflammation (arrow, inset). 20x objective.



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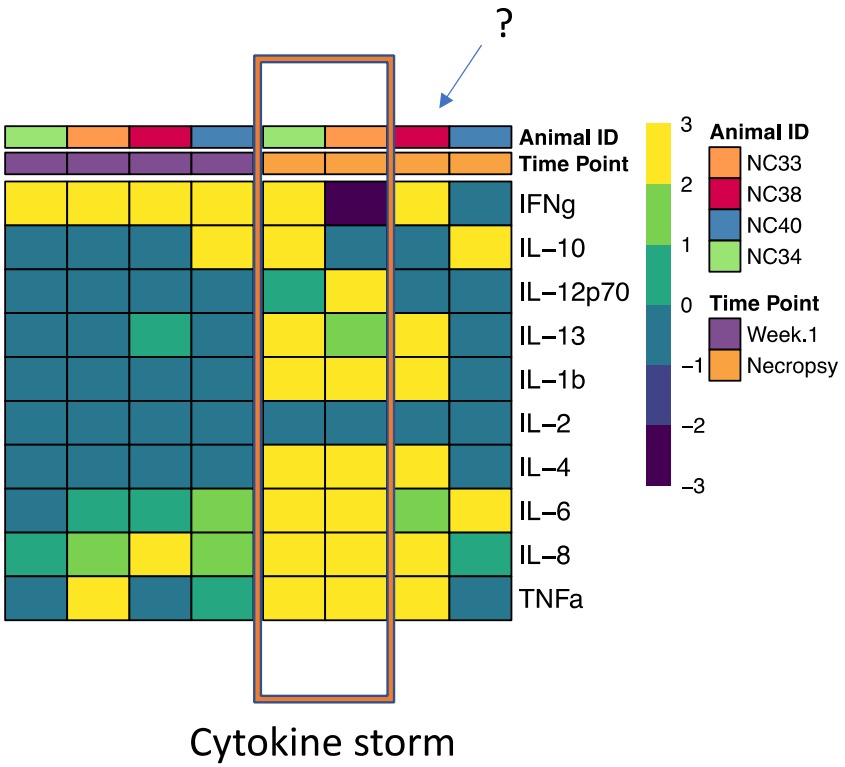
Nature Communications:

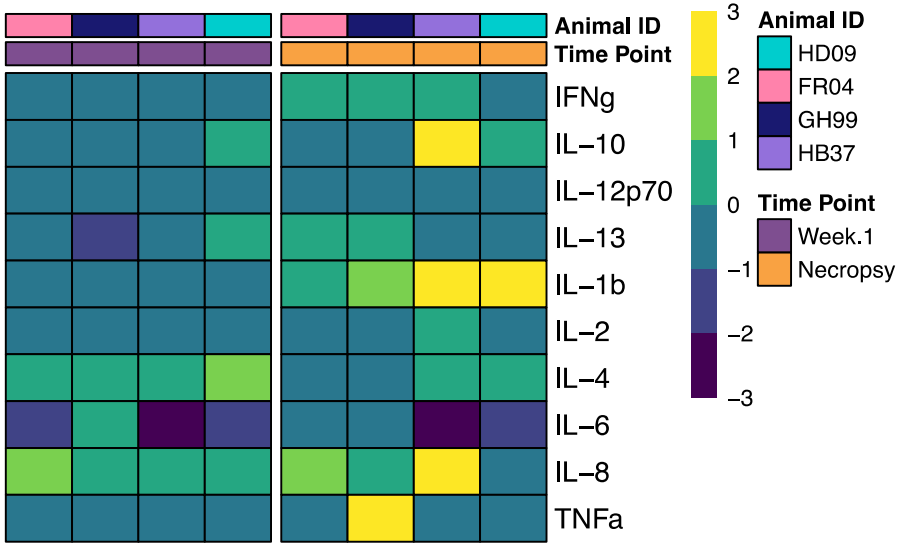
Cellular events of acute, resolving or progressive COVID-19 in SARS-CoV-2 infected non-human primates

MD Fahlberg, RV Blair, LA Doyle-Meyers, CC Midkiff, G Zenere, KE Russell-Lodrigue, CJ Monjure, EH Haupt, TP Penney, G Lehmicke, BM Threeton, N Golden, PK Datta, CJ Roy, RP Bohm, NJ Maness, T Fischer, J Rappaport, M Vaccari

doi: https://doi.org/10.1101/2020.07.21.213777

Cytokines and Cytokine Storm





African Green Monkeys

Rhesus macaques

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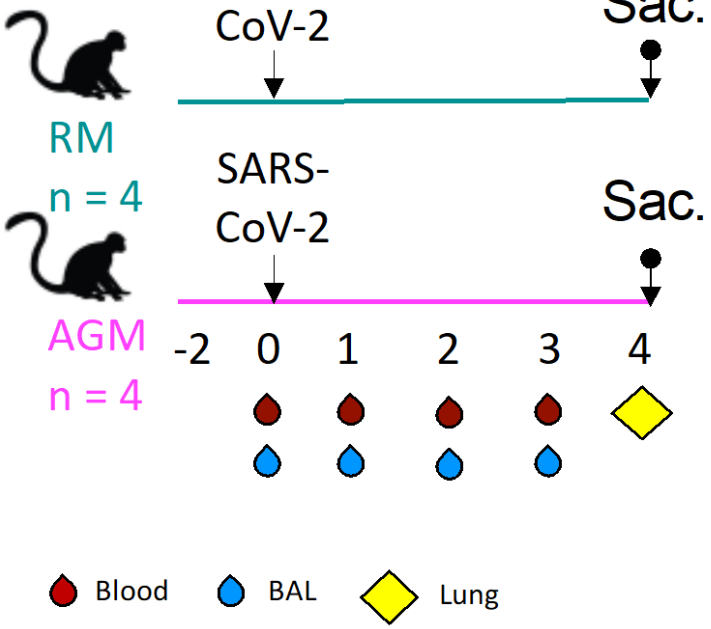
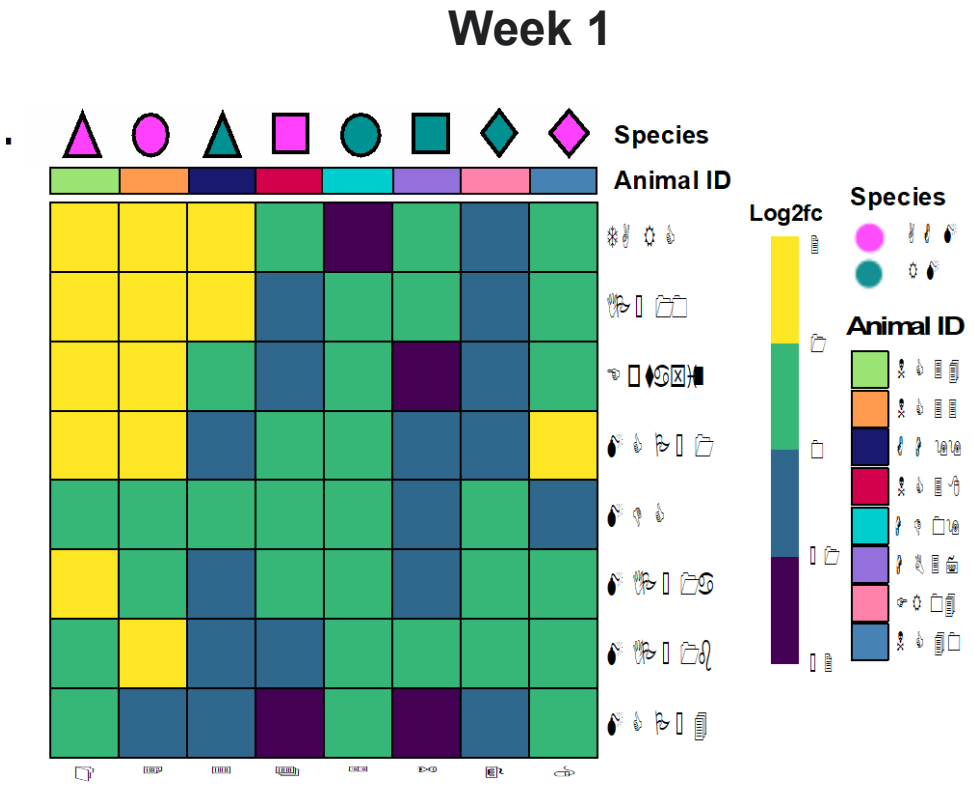
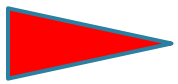
Chemokines plasma levels _COV-2 **Rhesus macaques** and **AGM**





Teal: Rhesus macaque (RM)

Pink: African Green Monkey (AGM)

More severe  Less severe

Monica Vaccari, TNPRC/Tulane

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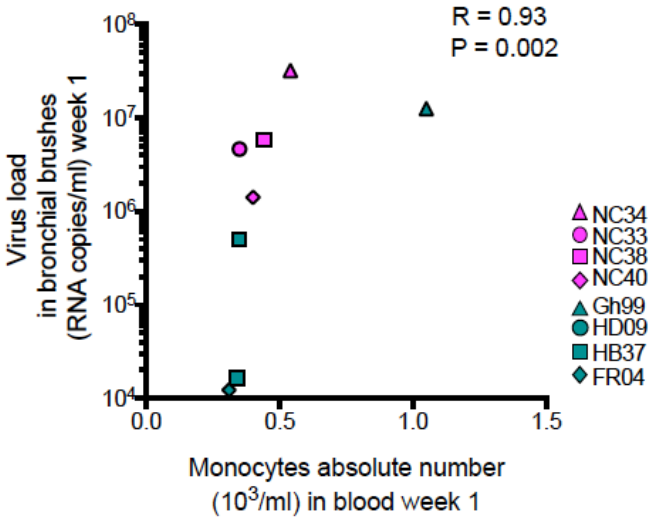
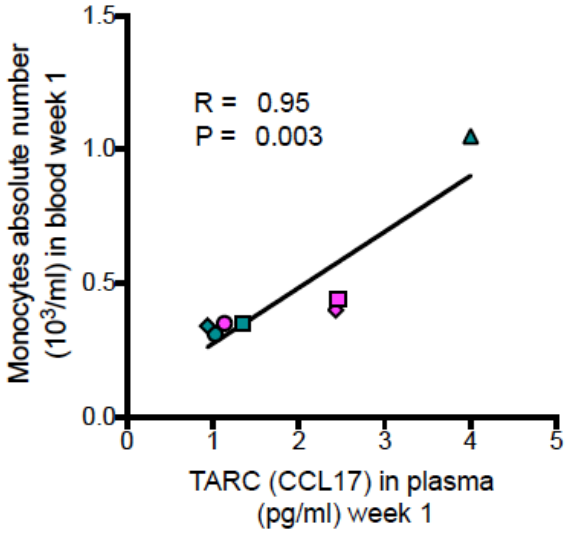
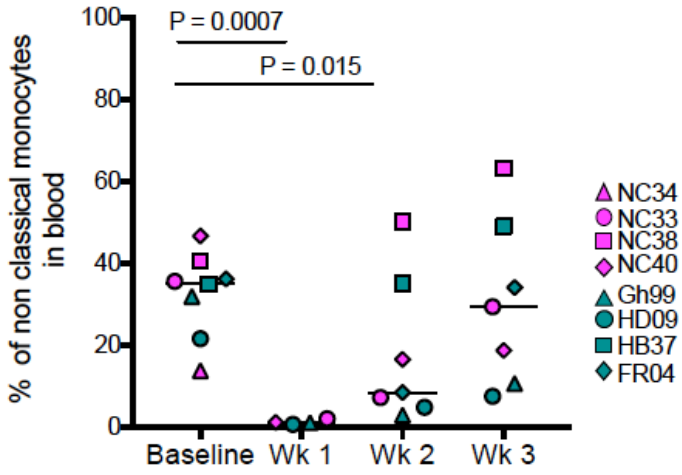
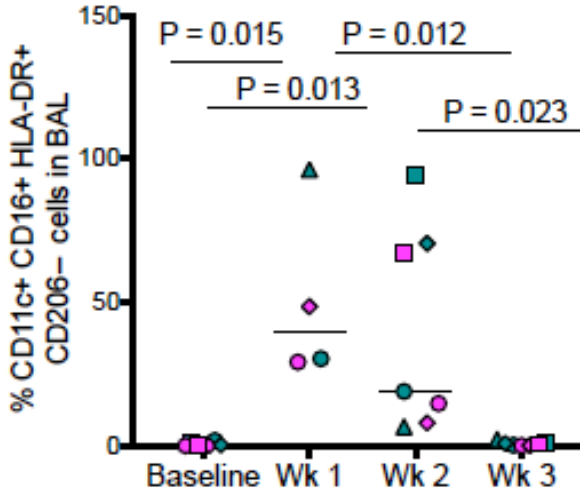
Monocyte Dynamics and Trafficking









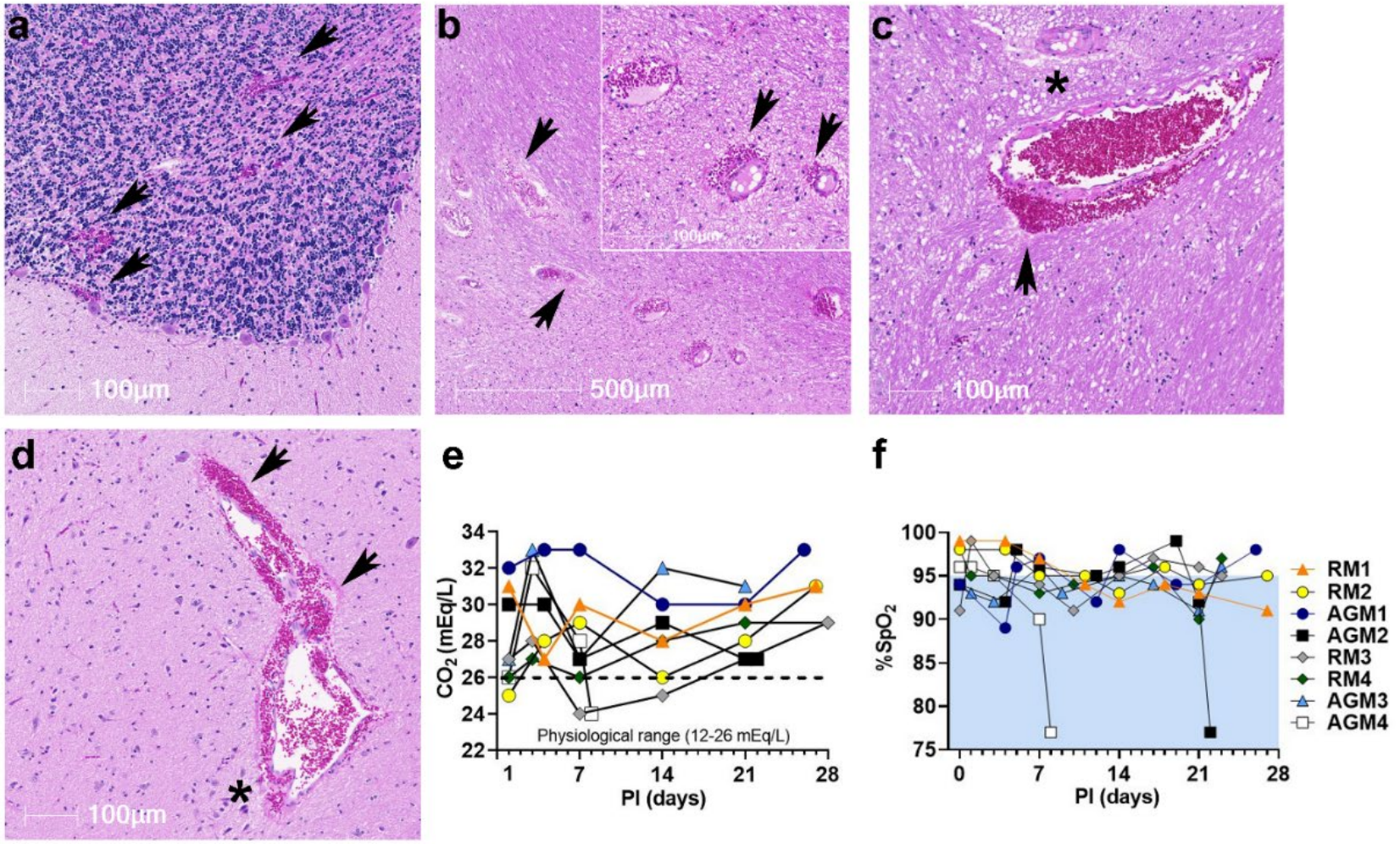
Monica Vaccari, TNPRC/Tulane

Nature Communication: In Revision

Neuropathology and Virus in Brain of SARS-CoV-2 Infected Non-Human Primates

Ibolya Rutkai[1], Meredith G. Mayer[2], Linh M. Hellmers[2], Bo Ning[3], Zhen Huang[3], Christopher J. Monjure[2], Carol Coyne[2], Rachel Silvestri[2], Nadia Golden[2], Krystle Hensley[2], Kristin Chandler[2], Gabrielle Lehmicke[2], Gregory J. Bix[1], Nicholas J. Maness[2], Kasi Russell-Lodrigue[2], Tony Y. Hu[3], Chad J. Roy[2], Robert V. Blair[2], Rudolf Bohm[2], Lara A. Doyle-Meyers[2], Jay Rappaport[2], and Tracy Fischer[2, *]

Microhemorrhages in CNS of SARS-CoV-2 infected NHPs



Neuropathology and Virus in Brain of SARS-CoV-2 Infected Non-Human Primates, Rutkai et al. (In Review)

Tracy Fischer, TNPRC/Tulane

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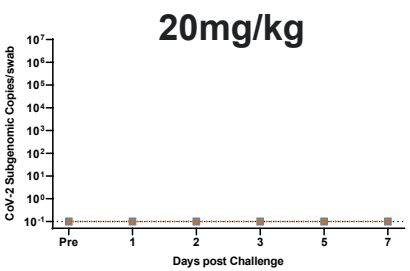
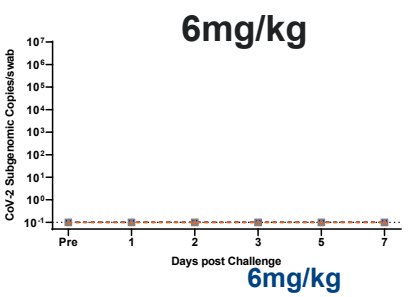
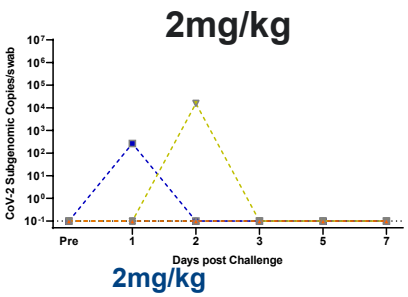
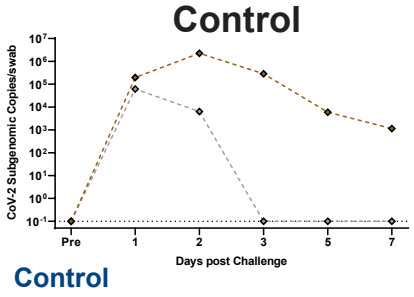
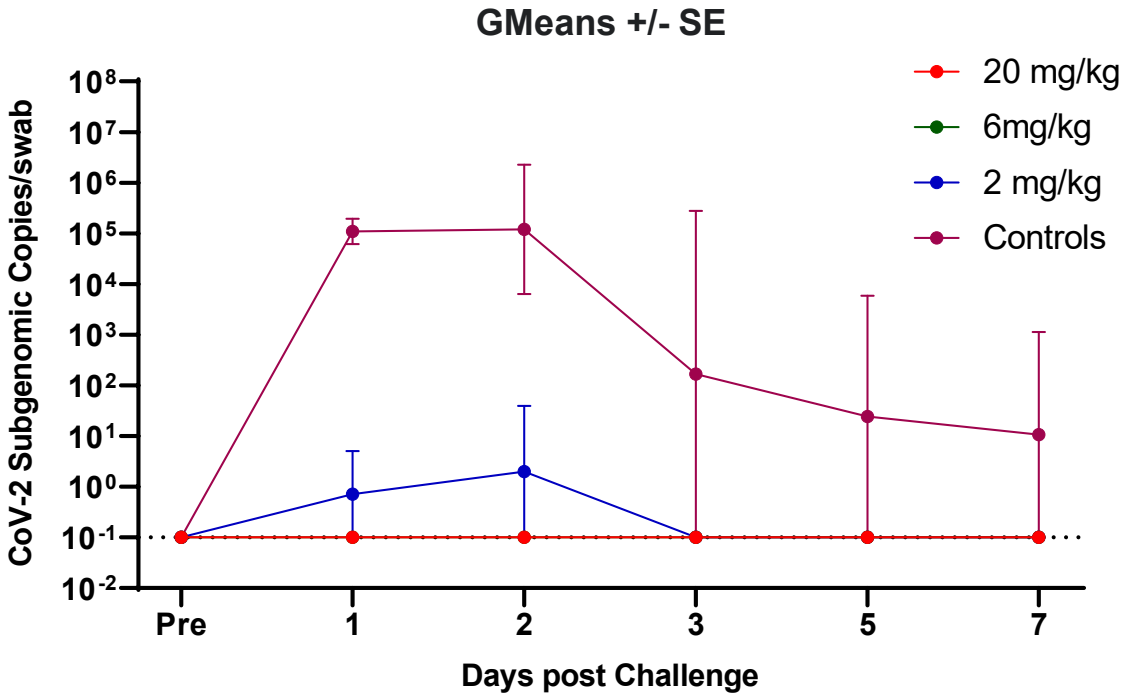
“Operation Warp Speed”: mAb Infusion and Day 3 Challenge – Pharyngeal Swabs











Chad Roy, Jean Patterson, Clint Florence, Michel Nussenzweig et al.

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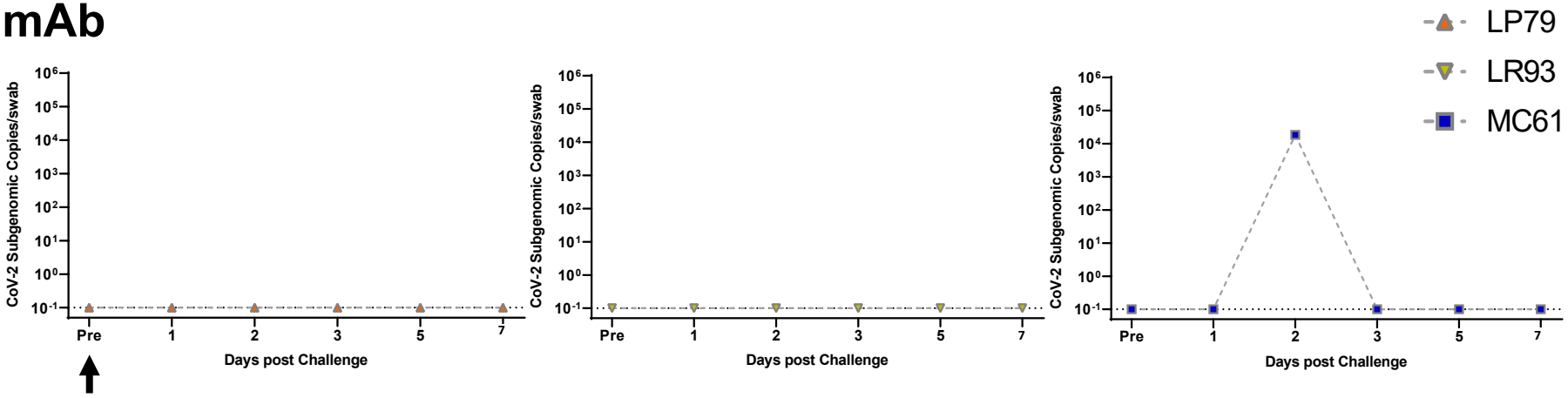
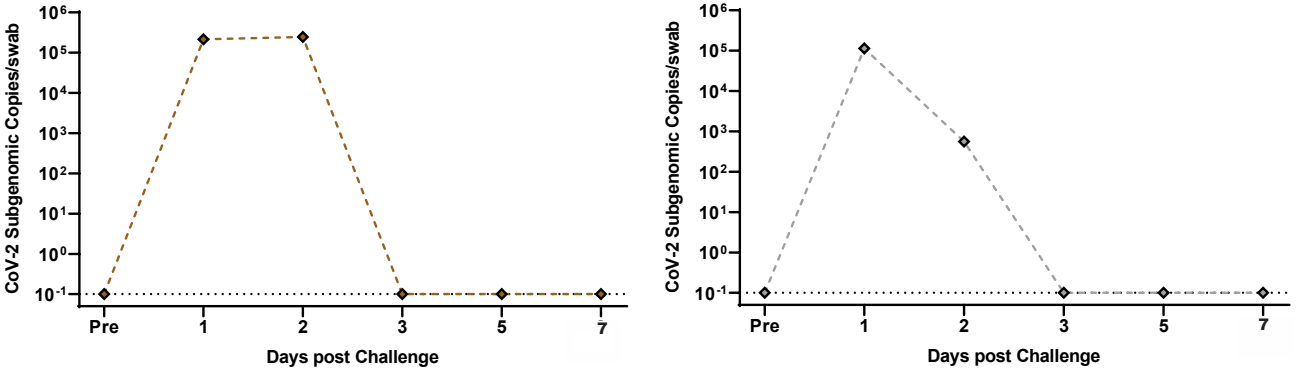
Delayed Challenge: 75 days! – Pharyngeal Swab

mAb



75 Days post Infusion

Controls



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CoVID-19 Conclusions

- We have developed animal models that will be useful for vaccine studies, antiviral testing, and therapeutics.
- A subset of aged African green monkey infected with SARS-CoV-2 recapitulated many of the disease manifestations including ARDS and cytokine storm.
- Immunologic studies emphasize the importance of monocytes/macrophages and cytokines produced by and/or affecting the migration of these cells/
- SARS-CoV-2 studies in NHP brain suggest damage to blood vessels and microhemorrhages.
- Passive antibody studies suggest the potential of monoclonal abs for significant SARS-CoV-2 prophylaxis

Summary (TNPRC)

- TNPRC is providing for the performance of vaccine studies for numerous platforms (foundation, biotech, and pharma).
- TNPRC performing studies in model development, immunology, and neuropathology for CoVID-19 research.
- TNPRC is performing passive antibody studies under OWS and and multiple vaccine and therapeutic studies.
- TNPRC is developing a National Coordinating Center for CoVID-19 Research for the NPRC System.

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Acknowledgements for COVID-19 RESEARCH

Robert V. Blair: Pathology
Lara A. Doyle
Chad J Roy
Tracy Fischer-Smith: Brain Pathology
Rudolf P. Bohm
Prasun K Datta
Nicholas J Maness
Monica Vaccari: Immune Studies
Antonito Panganiban
Ronald Veazey
Amitinder Kaur
Xuebin Qin

Containment and Quality Leadership

Angie Birnbaum**:** Director of Biocontainment Operations and Quality ProgramKarys Kenway: Quality Assurance Officer

Containment and Technical Staff

Chris Monjure- viral loads
Gabrielle Lehmicke- Lab manager

BSL-3 Core Staff

Nadia Golden- Sr. Research Coordinator
Breanna Threeton.
Toni Penney
Krystle Hensley

Jean Patterson, Clint Florence, Que Dang, Nancy Miller (NIH/NIAID/OWS), Sheri Hild (NIH/ORIP) and others.
Michel C. Nussenzweig, Rockeffer University, monoclonal antibody studies
Tom Hope, Northwestern University, antibody localization studies
Francois Villinger, New Iberia Research Center, multiple vaccine and localization studies.
Scott Weaver, Jessica A. Plante (UTMB)

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Funding for CoVID-19 Research

- Base grant and pilot program supported by
- P51 OD011104-59
- Brown Foundation
- “FAST GRANTS”: Monica Vaccari, Tracy Fischer
- NIAID/OWS Contract to Chad Roy
- Multiple studies in progress supported by pharma, foundation, and academia
- Seed funding from Tulane

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Questions?

SARS-CoV-2 |COVID-19

WSV WORLD SOCIETY FOR VIROLOGY

NEVER PANIC JUST MANAGE

https://www.ws-virology.org/ar/sars-cov2_covid_19-2/

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COVID RESEARCH AT THE NATIONAL PRIMATE RESEARCH CENTERS

Nancy L. Haigwood, Ph.D.

Why do research in primates?

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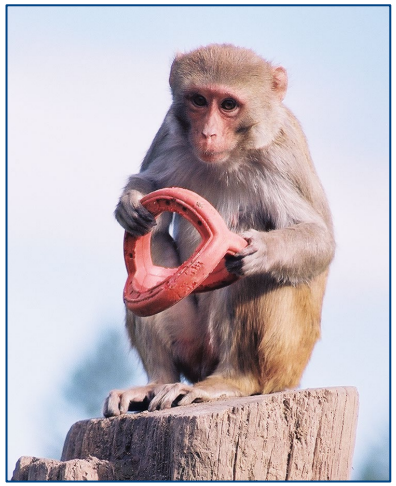
NIH established National Primate Research Centers in the 1960s to model human diseases

- Genetics, anatomy, physiology, reproduction, and immune responses similar to humans
- Pathogens frequently replicate and target similar organs and tissues
- Can measure complex cognitive and metabolic responses
- Longitudinal studies feasible that are not typically possible in clinical trials
- Same noninvasive imaging (PET, MRI, etc.) approaches as used in human patients
- Can test novel and innovative, but potentially 'risky' interventions, vaccines, therapies, cures



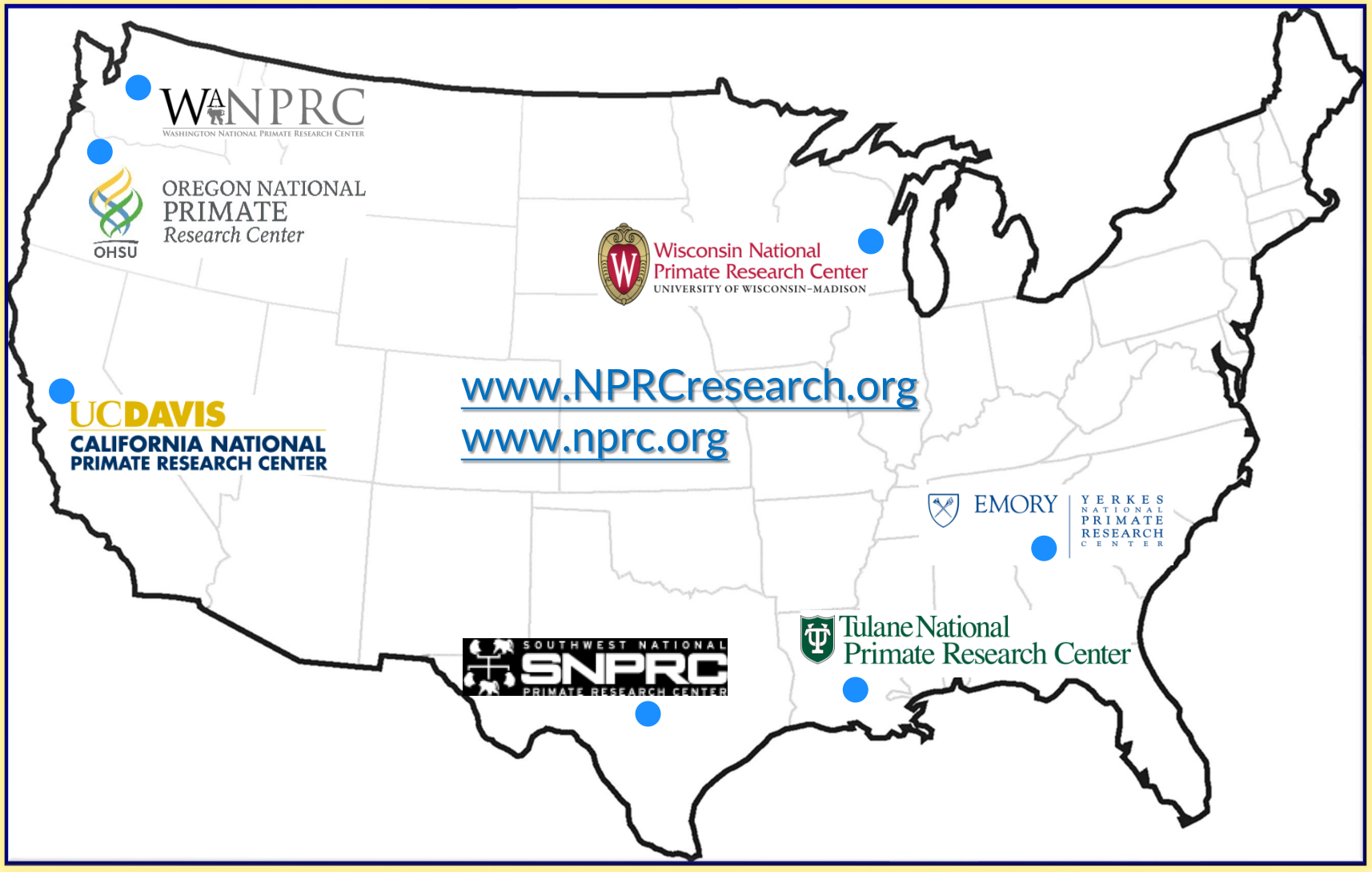
M. mulatta
Rhesus macaque
(*Indian & Chinese)*

M. nemestrina
Pigtail macaque

M. fascicularis
Cynomolgus macaque

Various NPRCs also have Japanese macaques, squirrel monkeys, baboons, chimpanzees, and marmosets

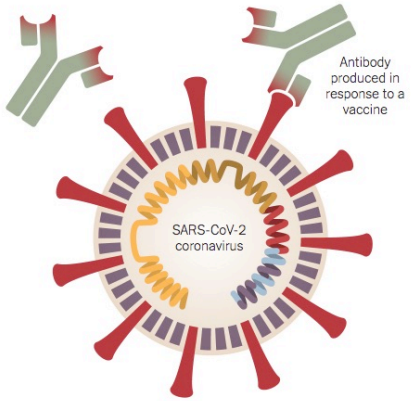
National Primate Research Center Consortium



The National Primate Research Centers (NPRCs) are a national network of dedicated teams fighting diseases from Alzheimer's to Zika and improving human health and lives worldwide

Rapid Response: Interdisciplinary and collaborative research can flow from co-localized expertise

How can the NPRCs contribute to solutions to the COVID-19 pandemic?



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ACTIV—Accelerating COVID-19 Treatments, Interventions, and Vaccines

ACTIV is a public-private partnership to develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines. Coordinated by the Foundation for the National Institutes of Health (FNIH), under the umbrella of Operation Warp Speed (OWS), **ACTIV brings NIH together with its sibling agencies in the Department of Health and Human Services**, including the Biomedical Advanced Research and Development Authority (BARDA), Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA); other government agencies including the Department of Defense (DOD) and Department of Veterans Affairs (VA); the European Medicines Agency (EMA); and **representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies**. (https://www.nih.gov/research-training/medical-research-initiatives/activ)

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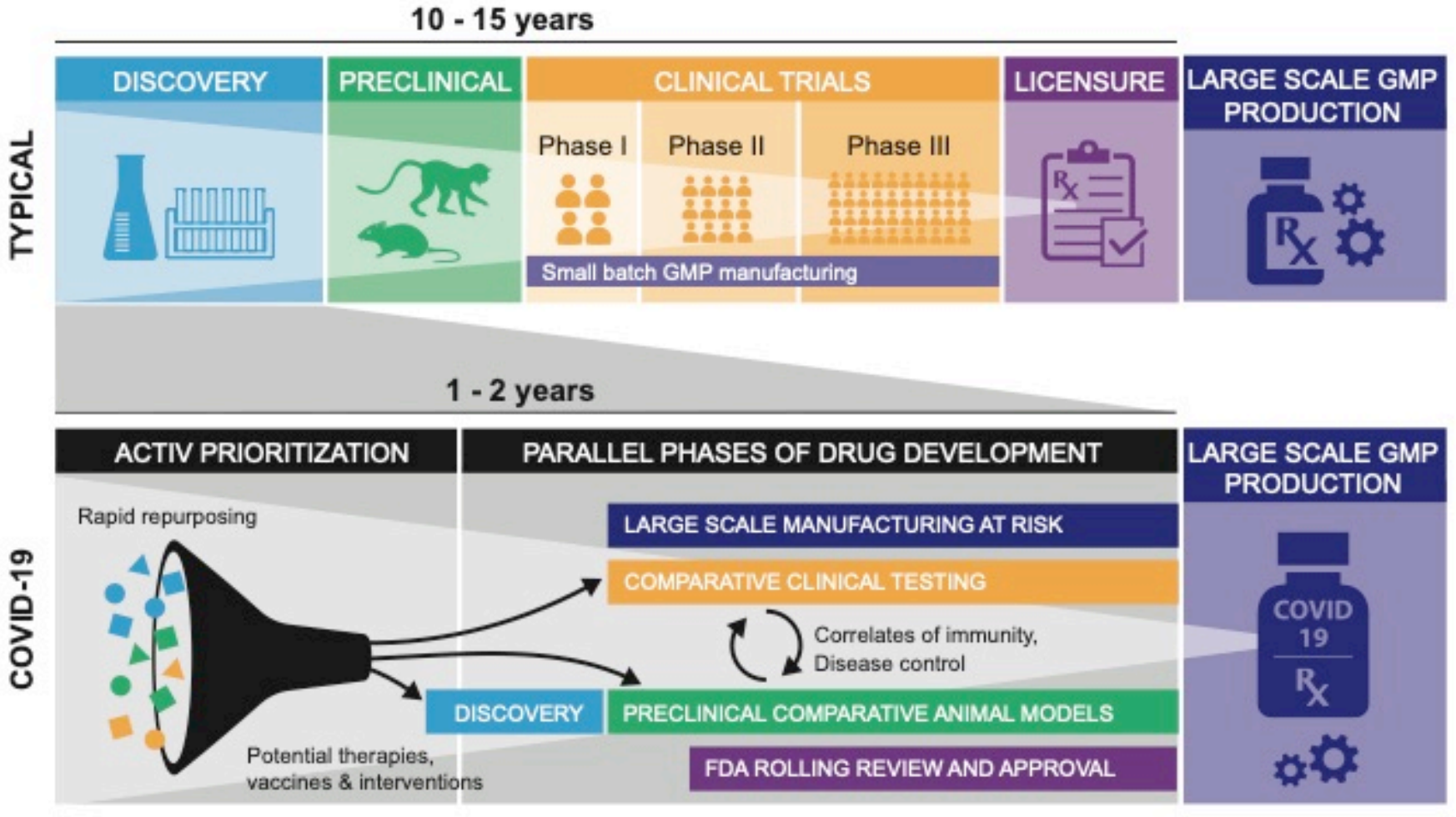
Accelerated Clinical Timeline for Vaccines, Therapies



Hewitt et al., 2020 ACTIVating Resources for the COVID-19 Pandemic: *In vivo* Models for Vaccines and Therapeutics, Cell Host & Microbe

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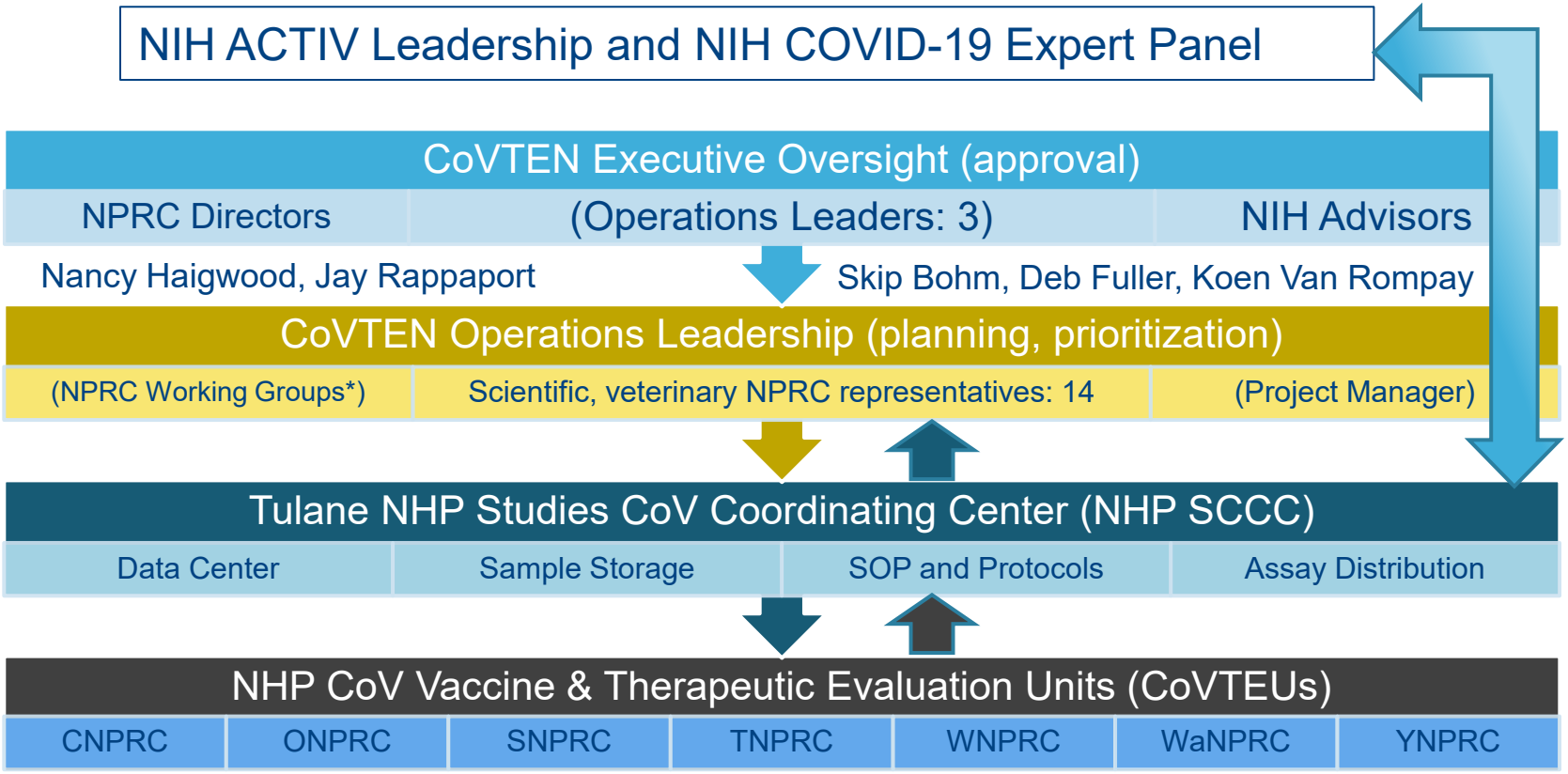
NPRC SARS-CoV-2 Vaccine and Therapeutic Evaluation Network (CoVTEN)



This network includes many outside experts from other universities, companies, and NIH

*Rigor & Reproducibility and Coronavirus working groups

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Why here? NPRC CoVTEN Rationale and Plans

- NPRCs are uniquely qualified due to deep immunology and virology expertise supported by HIV/AIDS dollars for decades
- NPRCs have well characterized SPF NHPs and BSL3 and ABSL3 space
- Work shared across the 7 NPRCs maximizes expertise, resources
- SARS-CoV-2 stocks will be made centrally, characterized, and shared
- Samples will be collected at the Tulane Coordinating Center
- Data collected at Data Center and results shared broadly
- Master Protocols and standard (centralized) assays shared by all NPRCs
- NHP Field Guide will be public

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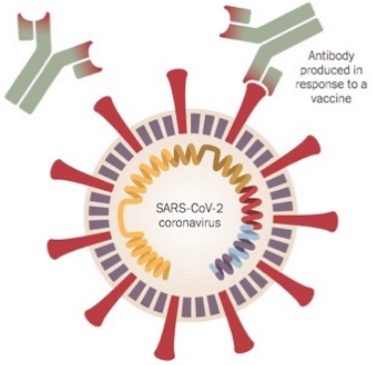
Nonhuman Primate Field Guide

Considerations for the use of primate models for SARS-CoV-2 treatments and vaccines

Prepared by the Coronavirus Vaccine & Treatment Evaluation Network
National Primate Research Centers
November 2020



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What about NHP resources for COVID research?

Primates are similar to the nursery business….requiring 3-4 years to mature. Planning is essential!

- NHP testing at NPRCs started in the summer of 2020
- NIH-funded COVID and other research (investigator-initiated) will continue at the same time, pending space and animal availability
- COVID-19 research will have the highest priority for NHP assignment until further notice
- NIH COVID-19 Expert Panel approves all NHP research to conserve resources for highest priority studies

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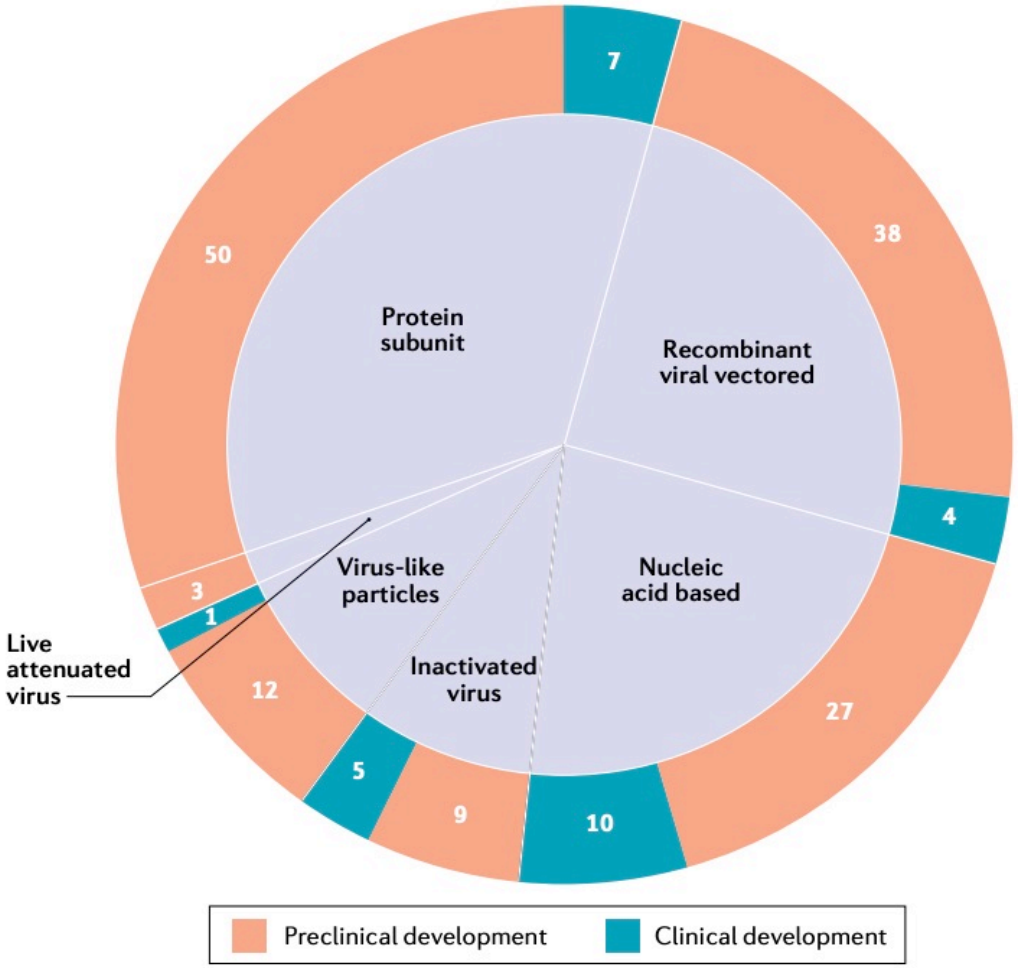
Global COVID vaccine landscape



Jeyanathan *et al., Immunological considerations for COVID-19 vaccine strategies*. Nature Reviews Immunology 2020

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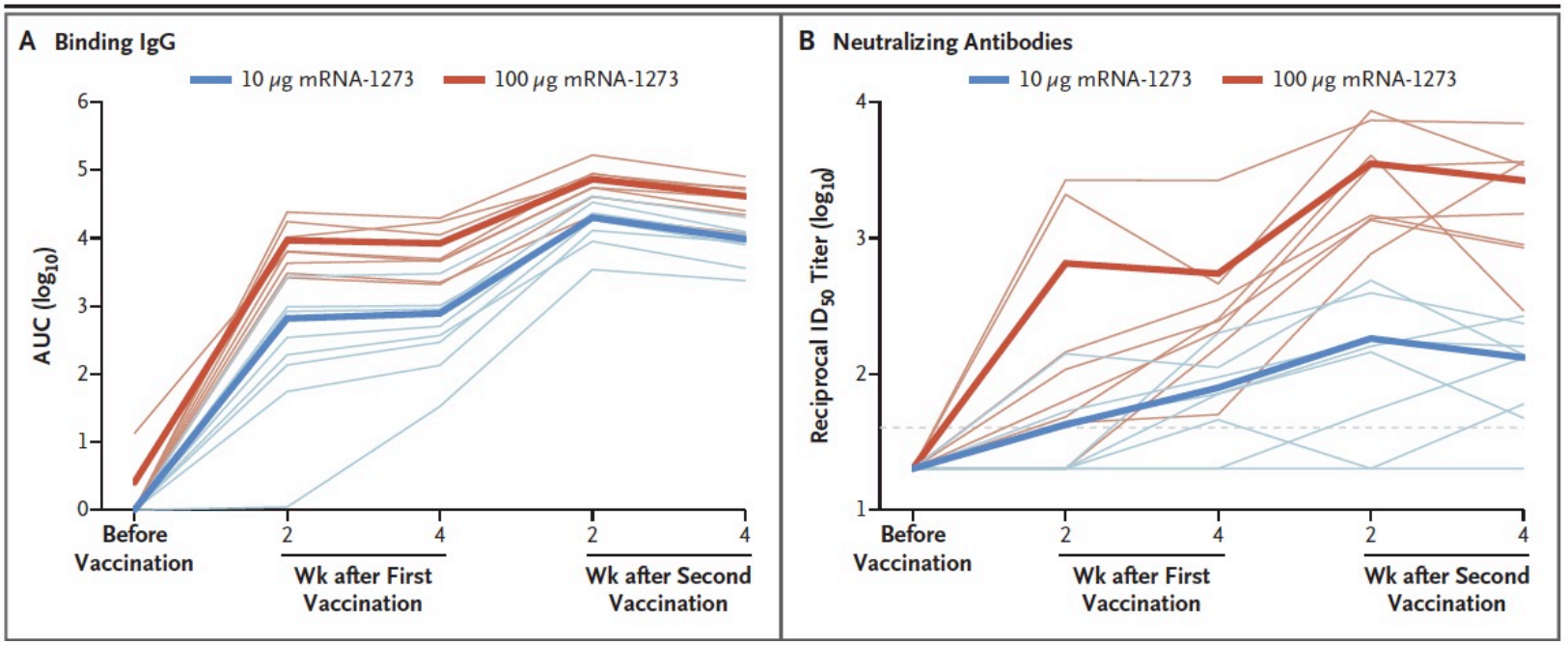
NHP research supporting mRNA-1273 COVID vaccines—Corbett et al., 2020 NEJM

Humoral immunity

VACCINE AGAINST SARS-COV-2 IN NONHUMAN PRIMATES



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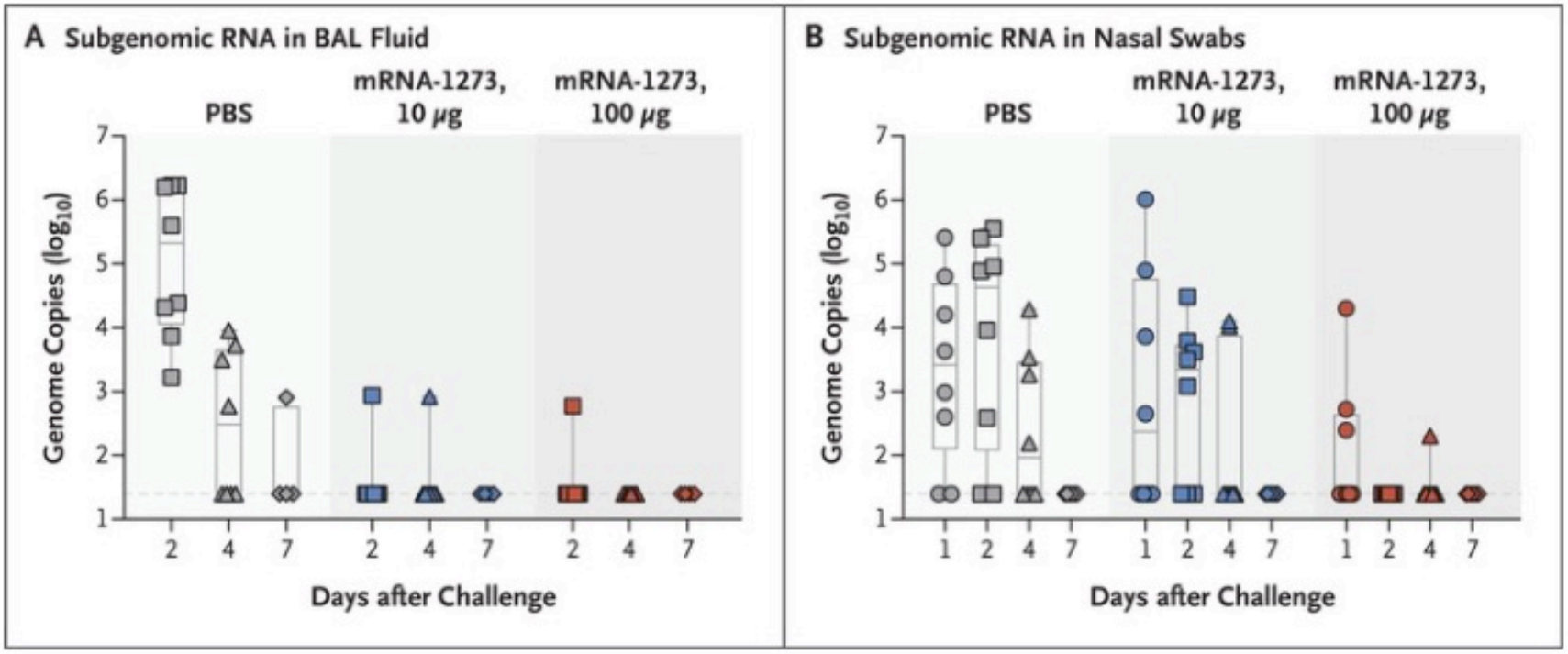
NHP research supporting mRNA-1273 COVID vaccines—Corbett et al., 2020 NEJM

Protection

Figure 3. Efficacy of mRNA-1273 against Upper and Lower Respiratory Viral Replication.



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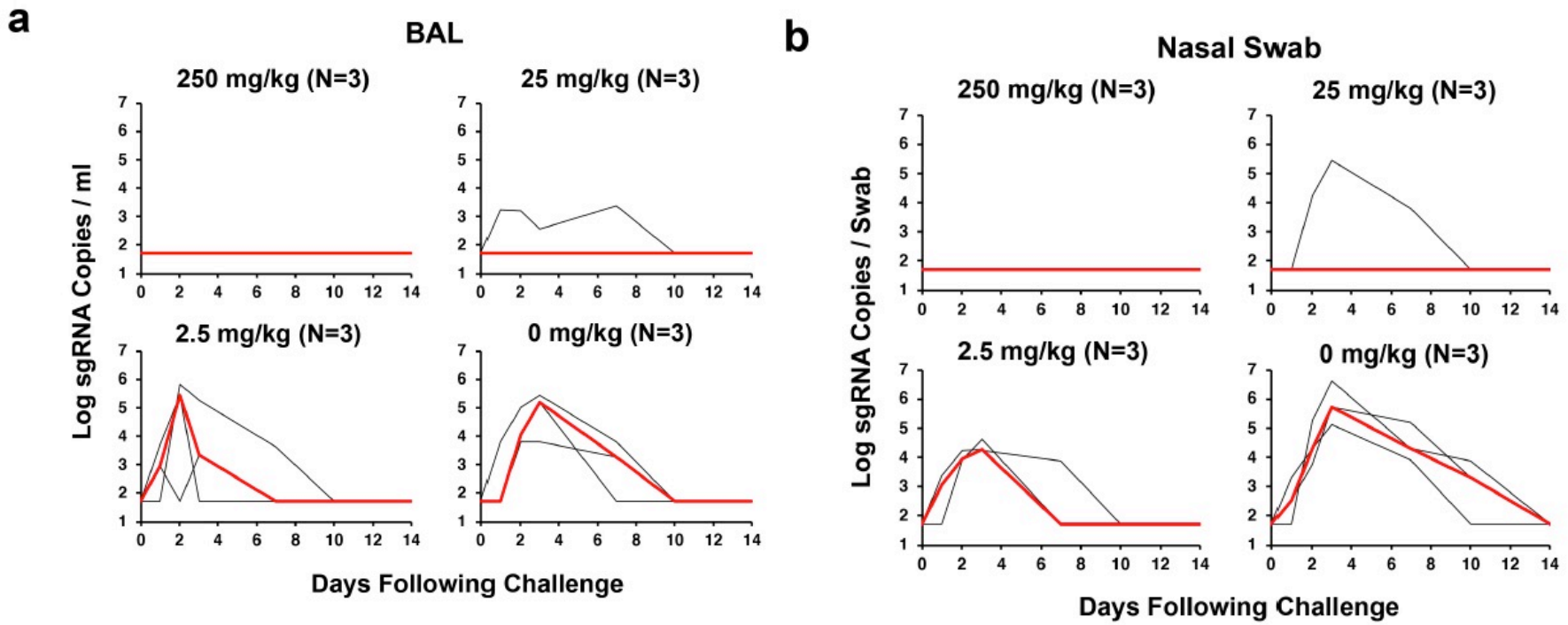
Correlates of protection against SARS-CoV-2 in rhesus macaques—McMahan et al., 2020 Nature

Pre-exposure IgG dose-response



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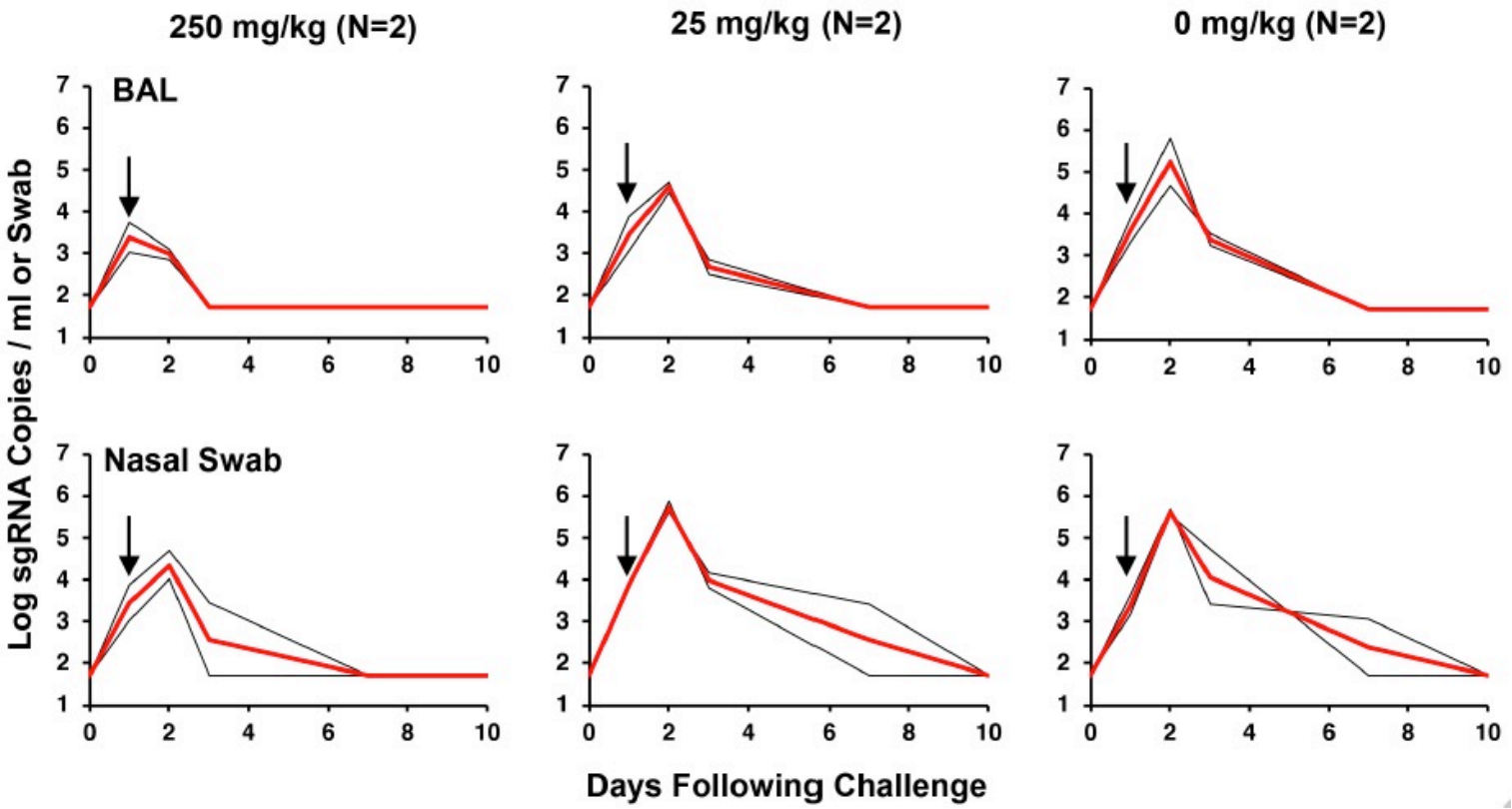
Correlates of protection against SARS-CoV-2 in rhesus macaques—McMahan et al., 2020 Nature

Post-exposure IgG dose-response



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Key questions for NHP testing

- Is there evidence for disease enhancement in the presence of preexisting immunity?—test with passive IgG and challenge
- Can more severe disease models be developed by ablating type I interferons?
- Can we model co-morbidities that result in greater disease severity (aging, diabetes, others)?
- Which combinations of monoclonal antibodies result in the most potent and longest-lasting protection?
- How can we use strategic growth for the future, for new outbreaks and pandemics?

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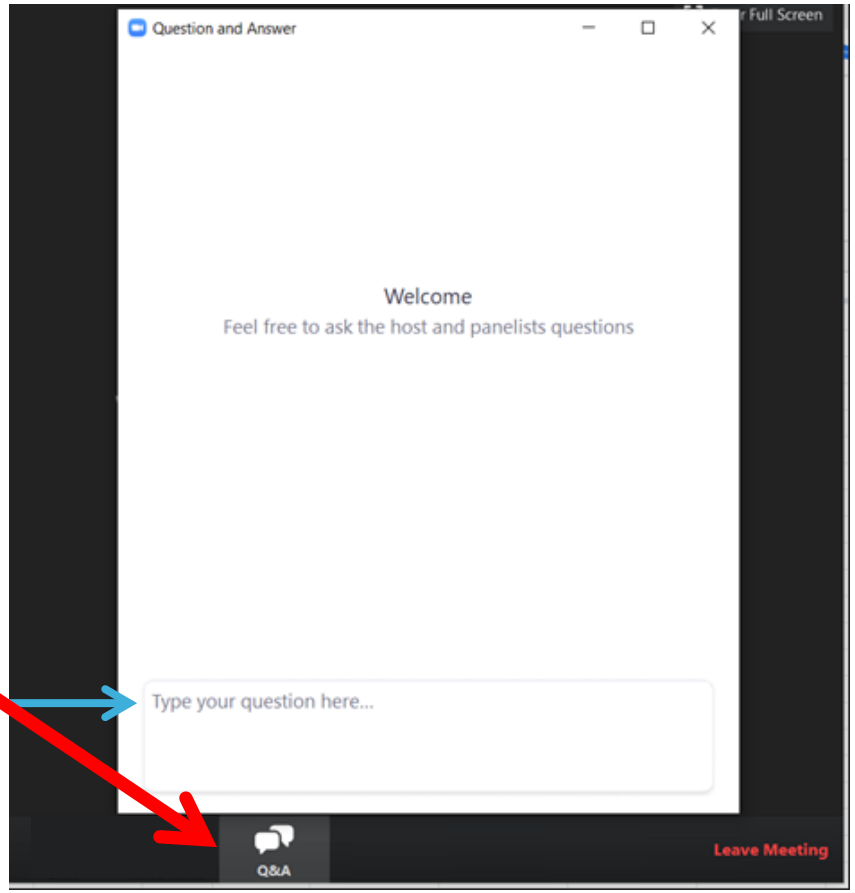
Questions for the Speakers

To Ask A Question

Click Q&A in the bottom tool bar

Type your question in the box



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Other Questions?

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NIH COVID19 Portals and Resources
[as discussed during the Q&A]

- COVID-19 NHP Study Information Portal https://redcap.ncats.nih.gov/redcap/surveys/?s=TLX93TDDMR
- NIH Guide Notice on “Notice of Limited Availability of Research Non-human Primates” (NOT-OD-20-173)
- NIH COVID19 Candidate and Technologies Portal: https://grants.nih.gov/grants/rfi/rfi.cfm?ID=107
- ACTIV COVID-19 Clinical & Preclinical Candidate Compound Portal: https://redcap.ncats.nih.gov/redcap/surveys/index.php?s=DAE87WPTE7

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